PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data:

9910366.5	6 May 1999 (06.05.99)	GB
0008179.4	5 April 2000 (05.04.00)	GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: COLCLOUGH, David [GB/GB]; Glaxo Wellcome plc, Temple Hill, Dartford, Kent DA1 5AH (GB). HODGSON, Anne [GB/GB]; Glaxo Wellcome plc, Temple Hill, Dartford, Kent DA1 5AH (GB). SZEWCZYK, Jerzy, Ryszard [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

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(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

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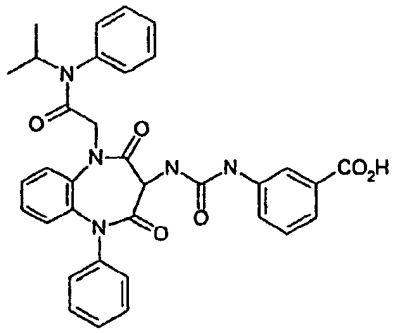
(54) Title: 1,5-BENZODIAZEPINE DERIVATIVES



(I)

(57) Abstract

An enantiomerically enriched compound of Formula (I) is disclosed, processes for its preparation, pharmaceutical compositions containing it and the use therefore, for the treatment of CCK-A mediated diseases or conditions, such as obesity.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agent: LEAROYD, Stephanie, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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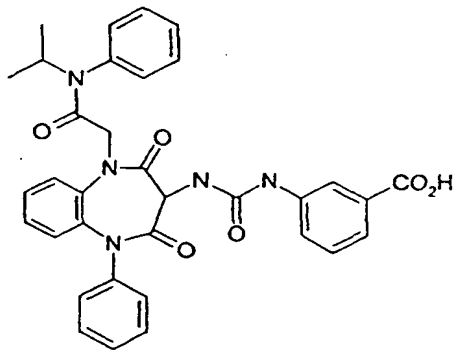
(88) Date of publication of the international search report:
1 March 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1,5-BENZODIAZEPINE DERIVATIVES AS CCK-A RECEPTOR AGONISTS



(I)

(57) Abstract: An enantiomerically enriched compound of Formula (I) is disclosed, processes for its preparation, pharmaceutical compositions containing it and the use therefore, for the treatment of CCK-A mediated diseases or conditions, such as obesity.

WO 00/68209 A3

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PU3611/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03982	04/05/2000	06/05/1999
International Patent Classification (IPC) or national classification and IPC C07D243/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/10/2000	27.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Traegler-Goeldel, M Telephone No. +49 89 2399 8278

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03982

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-8.

because:

☒ the said international application, or the said claims Nos. 5-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12

No: Claims

2. Citations and explanations
see separate sheet

re item III:

Claims 5 to 8 are directed to methods for the treatment of the human or animal body. Under the terms of Rule 67.1 (iv) and Article 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examinations on such claims with respect to industrial applicability.

re item V:

1. Prior art

The examining procedure is based on the document cited in the International Search Report:

J. Med. Chem. 1996; 39 (26); 5236-5245	D1
US-A 5646 140	D2
Annual Reports in Medicinal Chemistry 1990, Academic Press, Inc.; San Diego, p. 323-331	D3.

2. Novelty

The novelty of the enantiomerically enriched compound of claim 1 wherein it is not defined whether the enriched enantiomer is (+) or (-) is destroyed by the disclosure of compound 29 according to D1 and example 7 according to D2. Furthermore, even if claim 1 were formulated such that it concerned a enantiomerically enriched (+) enantiomer, document D2 has to be considered as novelty-destroying for the claimed subject matter, since it is sufficient for being considered as being disclosed that the compound may be identified without ambiguity as being individually intended and comprised in the document of the prior art. Not only the details of the prior art document given by examples have to be considered as disclosure, but the whole context of the prior art document. In the present case the mentioning of the enantiomers in the relevant document of the prior art is not limited to conceptual information about the existence of the enantiomers, but has to be considered as referring expressively to the fact that the single enatiomers are an integral part of the invention of the prior art. Document D2 does indeed mention in column 5, l. 30 to 41, explicitly that the invention according to

D2 includes all possible stereoisomers and geometric isomers of formula (I) and includes not only the racemic mixtures but also the optically active isomers as well and gives sufficient information for the skilled person as how to obtain a single enantiomer. Thus, clearly the single isomers are comprised by that document and example 7, being a racemic mixture of the claimed (+) enantiomer and the corresponding (-) enantiomer has thus to be considered as novelty-destroying for the claimed subject matter, since present claims 1 to 3 are formulated such that they do not exclude that the enantiomerically enriched (+) isomer is 100%. Therefore, the subject matter of claims 1 to 4 cannot be considered as being novel. The same applies for the methods of treatment according to claims 5 to 8 and the use of claim 9 depending on those claims and the analogy processes of claims 10 to 12 known from D1 and D2. Thus, the subject matter of claims 1 to 12 does not fulfil the requirements of Art. 33 (2) PCT.

3. Inventive step

Documents D1 and D2 are concerned with benzodiazepine derivatives being potent CCK-A agonists, disclosing, inter alia as one of the compounds showing the best activity the racemic mixture of the two enantiomers (compound 29 according to D1 and example 7 according to D2) comprised by the present subject matter. The present application discloses the enantiomerically enriched compound of example 7 according to D2 wherein the (+) enantiomer is enriched. The present application provides experimental data that the (+) isomer is more active than the (-) isomer, but not always more active than the racemic mixture in several tests, which is in line to the general disclosure in document D3 concerning stereochemistry in drug development.

The fact that the two enantiomers of the racemate of example 7 according to D2 show a CCK-A agonistic activity as well as the known racemic mixture (at least qualitatively the same activity as the parent compound example 7 according to D2) is considered to be an obvious solution to the problem of providing further CCK-A agonists and is also an obvious solution to the problem of providing further CCK-A agonists showing an unexpected effect as compared with the closest prior art, i.e. the racemate of example 7 according to D2 for the following reasons:

Even when it were presumed that the two isomers might antagonize each other, it is obvious that at least one of the isomers must be active, since the racemic mixture of

both isomers shows that activity, being a result of the action of both isomers. Presumed one isomer were inactive, it is obvious that the other one must be active since the racemic mixture as a whole is active. Thus, the skilled man would have expected either one or both of the isomers to be active, if the racemic mixture is active.

Furthermore the fact that either enantiomer may be more active than the other, no matter to what extent however, cannot be considered being a surprising feature, on which any inventive step may be based on, since first of all the pharmacological effect is the same as that of the racemate known from D2 and second, this does not contribute to either the enriched compound according to claim 1, nor to those according to claims 2 and 3 any technical feature due to which said compounds would show any unexpected effect as compared to the racemate of example 7 according to D2. The mere fact that a racemate has any medicinal activity does indeed mean that at least one of its enantiomeric components is active or even more active than the other one (see e.g. statement in document D3, p. 329, current trends: ....but if a racemate is active, many companies follow this with the screening of the individual enantiomer). Starting from the racemate of example 7 of the closest prior art D2, the problem underlying the present application which obviously has been solved is to be seen in the provision of further CCK-A agonists. But not only this solution, but also the solution of the problem of providing agents showing even a better activity as compared with the racemic mixture with increased physiologically activity from a physiologically active racemate must be considered as being obvious: It is generally known to specialists that in physiologically active substances with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, one of the latter frequently has a quantitatively greater effect than the other or the racemate. If , as it is the case here in the present application, the aim is therefore to develop agents with unexpected properties from a physiologically active racemate, the obvious first step is to produce the two enantiomers isolation and test whether one or the other is more active than the racemate. Such tests are routine. Since claims 1 to 3 are directed to the (+) enriched compound per se, the racemate of which is known and in the present case this known racemate is indeed in line with the general technical trend, the following considerations must be applied in the present case: the discovery of any potential unexpected effect of the enantiomers compared with corresponding racemates does not involve an inventive step. Whether one of the enantiomers is more effective than the racemate or the extent of any increased activity of one enantiomer

cannot be taken as an indication for any inventive step. To avoid any misunderstandings it is brought to the Applicant's attention that what has been considered for any pure enantiomer must of course apply for a compound enriched in the more active enantiomer as well. Thus the subject matter of claims 1 to 4 and of the depending claims 5 to 9 does not involve an inventive step. Claims 10 to 12 are obvious as well since they concern only analogy processes known from D1 and D2 or concern only conventional separations as already sufficiently known for the skilled person (see e.g. statement in document D3, p. 325, concerning the control of manufacture of enantiomerically pure chiral drugs).

Consequently, the subject matter of claims 1 to 12 does not fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No objection would arise if the claims were in accord with Art. 33 (2) and (3) PCT.

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date 09/98098

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PU3611/WO

Box No. I TITLE OF INVENTION

1,5-Benzodiazepine Derivatives

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).*

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☐ This person is also inventor.

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State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COLCLOUGH, David
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Kent
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This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).*

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Teleprinter No.: 25456

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to [illegible]ress to which correspondence should be sent.

Express Mail No.: EL395889843US

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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North Carolina 27709
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This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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State *(i.e. country)* of nationality:

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☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

☑ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☑ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☑ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☑ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*.....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

☑ **AE** United Arab Emirates
☑ **AL** Albania.....
☑ **AM** Armenia.....
☑ **AT** Austria.....
☑ **AU** Australia.....
☑ **AZ** Azerbaijan
☑ **BA** Bosnia and Herzegovina .....
☑ **BB** Barbados
☑ **BG** Bulgaria.....
☑ **BR** Brazil.....
☑ **BY** Belarus.....
☑ **CA** Canada
☑ **CH and LI** Switzerland and Liechtenstein
☑ **CN** China.....
☑ **CU** Cuba.....
☑ **CZ** Czech Republic.....
☑ **DE** Germany.....
☑ **DK** Denmark.....
☑ **EE** Estonia.....
☑ **ES** Spain.....
☑ **FI** Finland.....
☑ **GB** United Kingdom
☑ **GD** Grenada
☑ **GE** Georgia.....
☑ **GH** Ghana.....
☑ **GM** Gambia
☑ **HR** Croatia .....
☑ **HU** Hungary.....
☑ **ID** Indonesia
☑ **IL** Israel.....
☑ **IN** India.....
☑ **IS** Iceland
☑ **JP** Japan.....
☑ **KE** Kenya.....
☑ **KG** Kyrgyzstan.....
☑ **KP** Democratic People's Republic of Korea.....
☑ **KR** Republic of Korea.....
☑ **KZ** Kazakstan.....
☑ **LC** Saint Lucia
☑ **LK** Sri Lanka
☑ **LR** Liberia
☑ **LS** Lesotho.....
☑ **LT** Lithuania
☑ **LU** Luxembourg
☑ **LV** Latvia
☑ **MD** Republic of Moldova.....
☑ **MG** Madagascar.....
☑ **MK** The former Yugoslav Republic of Macedonia .....
☑ **MN** Mongolia
☑ **MW** Malawi.....
☑ **MX** Mexico.....
☑ **NO** Norway
☑ **NZ** New Zealand.....
☑ **PL** Poland.....
☑ **PT** Portugal.....
☑ **RO** Romania
☑ **RU** Russian Federation.....
☑ **SD** Sudan
☑ **SE** Sweden
☑ **SG** Singapore
☑ **SI** Slovenia.....
☑ **SK** Slovakia.....
☑ **SL** Sierra Leone
☑ **TJ** Tajikistan.....
☑ **TM** Turkmenistan.....
☑ **TR** Turkey.....
☑ **TT** Trinidad and Tobago.....
☑ **UA** Ukraine.....
☑ **UG** Uganda.....
☑ **US** United States of America.....
☑ **UZ** Uzbekistan.....
☑ **VN** Viet Nam.....
☑ **YU** Yugoslavia.....
☑ **ZA** South Africa
☑ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet.

☑ **AG** Antigua & Barbuda.....
☑ **CR** Costa Rica.....
☑ **DM** Dominica.....
☑ **DZ** Algeria.....
☑ **MA** Morocco.....
☑ **TZ** Tanzania.....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box

Filing Date of Earlier Application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 06 May 1999 (06.05.99)	9910366.5	GB		
item (2) 05 April 2000 (05.04.00)	0008179.4	GB		
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earli application was filed (Rue 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional office)*

Box. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	4
description (excluding sequence listing part)	27
claims	4
abstract	1
drawings	-
sequence listing part of description	
Total number of sheets	36

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s): (1) & (2)
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Stephanie Learoyd

Stephanie A Learoyd
Agent for the Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application
2. Drawings ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GLAXO WELLCOME PLC
Glaxo Wellcome House
Attn. LEAROYD, Stephanie A.
Berkeley Avenue
Greenford
Middlesex UB6 ONN
UNITED KINGDOM

Applicant's or agent's file reference PU3611/WO	Date of mailing (day/month/year) 10/11/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 00/ 03982	International filing date (day/month/year) 04/05/2000
Applicant GLAXO GROUP LIMITED	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer John De Bruijn

(July 1998)

Express Mail No.:
EL395889843US

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

cc R Bunn

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FILLER, Wendy A.
GLAXO WELLCOME PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
GRANDE BRETAGNE

30 APR 2001

MA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	27.04.2001
Applicant's or agent's file reference PU3611/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03982	04/05/2000	06/05/1999

Applicant
GLAXO GROUP LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel.+49 89 2399-8012

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